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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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WILMER CUTLER PICKERING HALE AND DORR LLP
60 STATE STREET
BOSTON, MA 02109

EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/828,975	REN ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-32,41,43,46,48,49,72 and 94* is/are pending in the application.

4a) Of the above claim(s) *41,43,46,48,49,72 and 94* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/31/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendment submitted December 7, 2005 is acknowledged.

Claims 1-28, 33-40, 42, 44, 45, 47, 50-71, 73-93, and 95-111 are canceled

Claims 29-32,41,43,46,48,49,72 and 94 are pending in the instant application.

Applicant's election of Group VI, claims 29-32, drawn to CatSper2 polypeptides, and the species of SEQ ID NO:2 and the epitope of residues 316-340 of SEQ ID NO:2 in the reply filed on December 7, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant has stated in the reply that the restriction requirement mailed September 7, 2005 does not indicate a relationship between Group VI and Groups X, XI, XVI, XIX, and XXIII and as such applicant believes that the other Groups are related to the instant invention and therefore they have been retained. Applicant further questions the non-inclusion of claim 41 in any Group.

Applicant is correct that the methods of Groups X, XI, XVI, and XXXIII as presented in the restriction requirement based upon the claims as amended February 18, 2005 all appear to make use of CatSper2 polypeptide and as such are related to Group VI as product and process of use, and apologizes for the oversight in paragraph 4 of the restriction requirement mailed September 7, 2005. Applicant is not correct in

indicating that the products of Group XIX, a contraceptive preparation that decreases CatSper2 activity, are related. Information to this effect can be found in paragraph 5 of the restriction requirement. Further, as set forth in paragraph 8, claim 41 is a linking claim that links the methods of Groups VIII-XV. As such, examination of the inventions of any one of Groups VIII-XV necessarily entails the examination of claim 41. The examiner apologizes if the standard form paragraphs do not make this point clear.

Claims 41,43,46,48,49,72 and 94 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 7, 2005 as explained above.

Claims 29-32 are under examination in the instant office action as they read on CatSper2 polypeptides comprising the species of amino acids 314-340 of SEQ ID NO:2.

Information Disclosure Statement

2. Applicant's IDS received March 31, 2005 has been acknowledged and considered by the examiner.

Priority

3. Applicant is requested to verify, and update as necessary, the status of any US application disclosed in the instant specification. Applicant is also reminded to update the first line of the specification to indicate that the instant application is a continuation of PCT/US02/33676 which claims priority to US provisional application 60/345,324.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 29, 31, and 32 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polypeptides comprising the sequence of SEQ ID NO:2 or fragments completely contained within the sequence of SEQ ID NO:2, does not reasonably provide enablement for a CatSper2 protein, fragments of a CatSper2 protein, or polypeptides 80% identical to a CatSper2 polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has claimed the genus of CatSper2 polypeptides and fragments thereof, and has disclosed the full length sequences of SEQ ID NO:2, SEQ ID NO:4, and SEQ ID NO:6 as members of this genus. SEQ ID NO:2 and 4 appear to be human splice variants, while SEQ ID NO:6 is disclosed as mouse CatSper2. The specification

defines the breadth of the term "CatSper2 protein" in paragraph 32 on page 32 wherein it is disclosed that CatSper2 proteins are sperm-specific cation channels and encompass SEQ ID NOs:2, 4, 6, allelic and splice variants of said SEQ ID numbers, and functional equivalents thereof. Note that allelic and splice variants and functional equivalents thereof reasonably include polypeptides 80% or more identical to SEQ ID NO:2, 4 or 6. The specification defines the activity of a CatSper2 protein to include induction of an ion current, mediation of Ca^{2+} influx, or the ability to complement the phenotype of CatSper2$^{-/-}$ sperm (see particularly paragraph 34 on page 11). Note that defining a protein by its ability to complement its absence is a circular argument that does not help a skilled artisan in identifying such a protein since one would already need to know the identity of the protein in order to generate the knockout cell line. Potential functional domains of CatSper2 are identified, such as transmembrane domains, pore region, and extracellular domains, based upon homology with known voltage-dependent ion channels (see particularly paragraphs 53, 54, 59, 60, and 179-182).

As indicated above, the term CatSper2 protein is broadly defined as being a sperm-specific cation channel. Such a definition reasonably indicates that other structurally distinct sperm- specific cation channel proteins, such as those disclosed by Ren et al. (reference AF on the IDS received March 31, 2005, see entire document, particularly Figure 1, (CatSper)) and Lobley et al. (Reprod Biol. Endocrinol. 2003, 1:53, see entire document, particularly Figures 1 and 2 (CatSper3 and CatSper4)) are encompassed by applicant's definition of a CatSper2 protein. The inclusion of variants

and functional equivalents expands the breadth of the term even further, and applicant has claimed polypeptides that are 80% identical to a CatSper2 protein. Skolnick et al. (Trends in Biotechnology, 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate and often unpredictable, in part because of the multifunctional nature of proteins (see particularly the Abstract and the section titled Sequence-based approaches to function prediction on page 34). Even in situations where there is some confidence of a similar overall structure between two sequences, only experimental research can confirm the artisan's best guess as to the function of the structurally related sequence (see in particular the Abstract and Box 2 on page 36). The complexity of the problem of assigning function based on homology rises as the percent similarity or identity falls (see Whisstock et al., Quarterly Reviews of Biophysics, 2003, 36:307-340, particularly the sentence that spans pages 321 and 323).

It is noted that the specification teaches specific functional domains of CatSper2, such as transmembrane or pore regions, based upon homology with other known ion channels. However, it appears that when the CatSper2 proteins of SEQ ID NOs:2, 4, and 6 were expressed in multiple cell types, either alone or in conjunction with the related CatSper protein, no changes in current or ion flux could be observed (see particularly Example 10 of the instant specification, Quill et al. (reference AE on the IDS received 3/31/05, see entire document, particularly the paragraph spanning pages 12530-12531), and Lobley et al. (see particularly the abstract)). As such, there does not appear to be any evidence that the sequences identified by the specification as

CatSper2 (i.e. SEQ ID NO:2, 4, and 6) actually function as sperm-specific cation channels. As such, it is not clear what functional activity a polypeptide 80% identical to SEQ ID NO:2, 4, or 6 would need to retain to be considered a CatSper2 polypeptide since the polypeptides of SEQ ID NO:2, 4, and 6 do not appear to have the disclosed functional property of being cation channels. Further note that the instant claims recite polypeptides that comprise only a portion or domain of a CatSper2 protein. Given that the full length proteins of SEQ ID NO:2, 4, and 6 do not appear to function as cation channels, polypeptides comprising only a portion or domain of said SEQ ID numbers certainly would not function as cation channels.

However, evidence does exist to indicate that CatSper2 is important for fertility since an infertile human patient has been identified who has a deletion in part of the CatSper2 gene located in chromosome 15q15 (Avidan et al., European Journal of Human Genetics, 2003, 11:497-502, see entire document). It is curious that the post-filing date art of Avidan et al. and the instant specification are discordant concerning the location of the CatSper2 gene, since the instant specification indicates that it resides on human chromosome 15q13 (see particularly paragraph 193 on page 59 of the instant specification). Therefore, while it is not certain that the polypeptides of SEQ ID NOs:2, 4, and 6 form functional cation channels, it is clear that the polypeptides of SEQ ID NO:2, 4, and 6 could be used to generate antibodies, said antibodies then being used to screen patients for infertility related to altered or defective expression of the proteins of SEQ ID NO:2, 4 or 6. Colman (Research in Immunology, 1994, 145:33-36) teaches that even single amino acid changes in an antigen can completely disrupt the binding

between an antibody and an antigen (see particularly the paragraph that starts in the right column of page 33). As such, CatSper2 proteins that are less than 100% identical to the sequences of SEQ ID NO:2, 4, or 6 can elicit an antibody response wherein the elicited antibodies are not capable of binding to the wild-type CatSper2 proteins of SEQ ID NO:2, 4, and 6. The specification does not appear to disclose a utility for antibodies that cannot bind the wild-type CatSper2 sequences of SEQ ID NOs:2, 4, or 6, and as such the polypeptides that can be used to generate said antibodies do not appear to be enabled.

Therefore, given the breadth of the term "CatSper2 protein" as defined by the specification, the fact that the disclosed sequences of SEQ ID NO:2, 4, and 6 do not appear to act as cation channels as evidenced by Example 10 of the specification and the art of Quill et al. and Lobley et al., the fact that only experimental evidence can confirm functional similarity of sequences related by a given percent identity or homology as taught by Skolnick et al. and Whisstock et al., and the fact that while CatSper2 polypeptides can be used to generate antibodies, antibodies generated against sequences of less than 100% identity may not bind the wild-type sequence as taught by Colman and the specification does not appear to provide a use for antibodies that bind CatSper2 sequence other that those of SEQ ID NO:2, 4, and 6, and thus the polypeptides used to generate such antibodies also do not appear to have a disclosed use, a skilled artisan would not be able to make and use the full breadth of applicant's claimed invention without first conducting additional research.

6. Claims 29, 30, and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of the proteins of SEQ ID NOs:2, 4, and 6.

Applicant is not in possession of the genus of all CatSper2 proteins, proteins 80% identical to a CatSper2 protein, or proteins comprising fragments 80% identical to a CatSper2 protein.

Applicant has broadly claimed CatSper2 proteins, proteins comprising fragments of a CatSper2 protein, proteins 80% identical to a CatSper2 protein, and proteins containing fragments that are 80% identical to a CatSper2 protein. To support this genus, applicant has disclosed the proteins of SEQ ID NO:2, 4, and 6. Applicant has identified particular domains of CatSper2 based upon homology with other known cation channels. Skolnick et al. (Trends in Biotechnology, 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate and often unpredictable, in part because of the multifunctional nature of proteins (see particularly the Abstract and the section titled Sequence-based approaches to function prediction on page 34). Even in situations where there is some confidence of a similar overall structure between two sequences, only experimental research can confirm the artisan's best guess as to the function of the structurally related sequence (see in particular the Abstract and Box

2 on page 36). The complexity of the problem of assigning function based on homology rises as the percent similarity or identity falls (see Whisstock et al., Quarterly Reviews of Biophysics, 2003, 36:307-340, particularly the sentence that spans pages 321 and 323). As such, it is not clear that the domains identified by applicant actually have their disclosed functions. This is especially true since the full length proteins of SEQ ID NO:2, 4, and 6 failed to demonstrate the disclosed functional activities of induction of ion currents or mediation of Ca^{2+} transport when expressed by themselves or in conjunction with additional proteins as shown in Example 10 and the teachings of Quill et al. (reference AE on the IDS received 3/31/05, see entire document, particularly the paragraph spanning pages 12530-12531). As such, there does not appear to be any disclosed link between the structure of the molecule and its functional properties.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3). As discussed above, the domains or regions of the claimed CatSper2 proteins that are critical for function and must be maintained are not defined by the specification, nor

are regions that can be successfully modified without influencing function defined given that even the full length proteins of SEQ ID NO:2, 4, and 6 failed to demonstrate the functional characteristics of an ion channel when transfected into a cell. In light of this, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus of CatSper2 proteins, proteins comprising fragments of CatSper2 proteins, proteins 80% identical to a CatSper2 protein, and proteins containing fragments that are 80% identical to a CatSper2 protein. Thus, Applicant was not in possession of the claimed genus of all CatSper2 proteins, proteins comprising fragments of CatSper2 proteins, proteins 80% identical to a CatSper2 protein, and proteins containing fragments that are 80% identical to a CatSper2 protein. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 29-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Rosen et al. (WO 00/61624 A1, of record on the IDS received March 31, 2005, see entire document).

Rosen et al teach a polypeptide that is 100% identical to amino acids 108-350 of SEQ ID NO:2 of the instant invention (see entire document and the enclosed copy of the sequence search notes). Based upon the teachings in the specification found on pages 18-19 of the instant specification, the polypeptide taught by Rosen et al. comprises transmembrane domains, extracellular loops, a pore, and antigenic epitopes of a CatSper2 polypeptide. Note that the polypeptide of Rosen et al. encompasses the elected epitope of residues 316-340 of SEQ ID NO:2. It should also be noted that the definition of CatSper2 activity as defined in paragraph 34 found on page 11 includes activity as a calcium ion channel, and the polypeptide taught by Rosen et al. is disclosed to be a calcium channel expressed in human testes (see particularly pages 57 and 58 of Rosen et al.).

Therefore, the prior art anticipates the claimed invention.

9. No claims are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael Szperka, Ph.D.
Patent Examiner
Technology Center 1600
February 15, 2006

Patrick J. Nolan, Ph.D.
Primary Examiner
Technology Center 1600